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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WEIMIN SUN and FERAS HANTASH

Appeal 2009-0008117
Application 10/754,446
Technology Center 1600

Decided: November 18, 2009

Before DONALD E. ADAMS, MELANIE L. McCOLLUM, and JEFFREY N. FREDMAN, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to detection of a deletion mutation associated with Mucolipidosis Type IV. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"Mucolipidosis Type IV (ML IV) is a rare, neurodegenerative, autosomal recessive disorder. ML IV is a lysosomal storage disease that results in the excessive transport of membrane components (mucopolysaccharides and lipids) to lysosomes compared with normal cells" (Spec. 1 ¶ 0003). According to the Specification, "[a]n A>G transition (IVS 3-2 A>G), which causes a splice site mutation in the acceptor site of intron 3 is found in 72% of Ashkenazi ML IV alleles" (Spec. 1 ¶ 0004). The Specification teaches that a "6.4 kb deletion that includes exons 1 to 7 of the MCOLN1 gene (GenBank accession no. AF287270) is found in 23% of Ashkenazi ML IV alleles. See e.g., Bach (2001) *Molecular Genetics and Metabolism* 73:197-203" (Spec. 1 ¶ 0004).

The Claims

Claims 19-34 are on appeal. Claims 19, 20, 25, and 31 are representative and read as follows:

> 19. A method of determining the presence of a Mucolipidosis IV deletion mutation sequence in a nucleic acid, comprising,
>
> a) contacting the nucleic acid with:
>
> i) a first oligonucleotide primer that comprises a sequence complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene (SEQ ID NO: 8),
>
> ii) a second oligonucleotide primer that comprises a sequence complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene (SEQ ID NO: 8), and
>
> iii) an oligonucleotide probe that comprises a sequence complementary to a 13-30 bp segment of a

fragment that is amplified using the first and second primer, wherein said probe is labeled with a detectable label which comprises a donor fluorophore and a quencher moiety, wherein said quencher moiety is optionally an acceptor fluorophore; and

b) conducting amplification by temperature cycling and monitoring the accumulation of amplified nucleic in real time by detecting an increase in donor fluorophore fluorescence or a decrease in acceptor fluorophore fluorescence which indicates the presence of the Mucolipidosis IV mutant sequence in the nucleic acid.

20. The method of claim 19 wherein the first oligonucleotide primer comprises a sequence that consists essentially of 5'-CTT GCT CTG TTG CCC AGG CT -3' (SEQ ID NO. 3).

25. A method of detecting the presence of one or two Mucolipidosis IV mutant sequences in a nucleic acid, comprising,

a) contacting the nucleic acid with:

i) a first oligonucleotide primer that comprises a sequence complementary to a 15-30 bp segment of DNA between positions 5124-5524 of the MCOLN1 gene (SEQ ID NO: 8),

ii) a second oligonucleotide primer that comprises a sequence complementary to a 15-30 bp segment of DNA between positions 5541-5941 of the MCOLN1 gene (SEQ ID NO: 8),

iii) a first oligonucleotide probe that comprises a sequence complementary to a 13-30 bp segment of a fragment that is amplified using the first and second oligonucleotide primers, wherein said first oligonucleotide probe includes position 5534 of the MCOLN1 gene (SEQ ID NO: 8), wherein said first

oligonucleotide probe is labeled with a first detectable label which comprises a donor fluorophore and a quencher moiety, wherein said quencher moiety is optionally an acceptor fluorophore:

iv) a third oligonucleotide primer that comprises a sequence complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene (SEQ ID NO: 8),

v) a fourth oligonucleotide primer that comprises a sequence complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene (SEQ ID NO: 8), and

vi) a second oligonucleotide probe that comprises a sequence complementary to a 13-30 bp segment of a fragment that is amplified using the third and fourth primers, wherein said probe wherein said second oligonucleotide probe is labeled with a second detectable label which comprises a donor fluorophore and a quencher moiety, wherein said quencher moiety is optionally an acceptor fluorophore, and wherein said second detectable label is distinguishable from said first detectable label; and

b) conducting amplification by temperature cycling and monitoring the accumulation of amplified nucleic in real time by detecting an increase in donor fluorophore fluorescence or an increase or decrease in acceptor fluorophore fluorescence, which indicates the presence of one or both of the Mucolipidosis IV mutant sequences in the nucleic acid, wherein said first and second primer and first probe detect a single base transition mutation and said third and fourth primer and second probe detect a deletion mutation.

> 31. The method of claim 25 wherein the second probe comprises a sequence that consists essentially of 5'- AGACC CAG GCC CAC AT- 3' (SEQ ID NO: 7).

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Edelmann et al., *Carrier Screening for Mucolipidosis Type IV in the American Ashkenazi Jewish Population*, 70 AM. J. HUMAN GENETICS 1023-7 (2002).

Mark A. Doll and David W. Hein, *Rapid Genotype Method to Distinguish Frequent and/or Functional Polymorphisms in Human N-Acetyltransferase-1*, 301 ANALYTICAL BIOCHEMISTRY 328-32 (2002).

Buck et al., *Design Strategies and Performance of Custom DNA Sequencing Primers*, 27 BIOTECHNIQUES 528-36 (1999).

GenBank AF287270, *Homo sapiens mucolipin (MCOLN1) gene, complete cds*, 1-5 (2000).

The issues

A. The Examiner rejected claims 19, 23-25, 28, and 32-34 under 35 U.S.C. § 103(a) as obvious over Edelmann, Genbank and Doll (Ans. 3-6).

B. The Examiner rejected claims 20-22, 26, 27, and 29-31 under 35 U.S.C. § 103(a) as obvious over Edelmann, Genbank, Doll and Buck (Ans. 7-8).

A. 35 U.S.C. § 103(a) over Edelmann, Genbank and Doll

The Examiner finds it obvious to

> have modified the mutation detection methods of Edelmann et al to have used the real time PCR detection methods of Doll et al et al [sic]. One would have been motivated to do

> so based on the assertion by Doll et al that the real time PCR based method is a rapid method for the analysis of nucleic acid sequences that is reliable, does not require radioactivity, and is suitable for automated applications

(Ans. 6).

Appellants argue that "[n]either Edelmann et al. nor Doll et al. teach or suggest a method for the real-time detection of a deletion mutation in the MCOLN1 gene as required by claim 19" (App. Br. 8). Appellants argue that "[t]he Examiner fails to demonstrate that the prior art provides a motivation to combine the methods of Edelmann et al. and Doll et al. in an attempt to derive the method of claim 19." (*Id.*)

Appellants also argue that "the combination Edelmann et al. and Doll et al. fails to teach, and provides no reasonable expectation that multiple types of mutations (i.e., point mutations and deletion mutations) can be simultaneously detected on multiple amplicons in a real-time PCR-based assay as recited in claim 25" (*id.* at 10).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Have Appellants demonstrated that the Examiner erred in finding it obvious to utilize the real-time PCR assay of Doll to detect the deletion and point mutations in the MCOLN1 gene disclosed by Edelmann?

Findings of Fact (FF)

1. Edelmann teaches that "[r]ecently, the gene that is mutated in patients with MLIV [Mucolipidosis Type IV], MCOLN1 . . . was isolated, and the two AJ founder mutations were identified. These mutations were (1)

a splicing mutation IVS3-2A→G . . . and (2) a 6,434-bp deletion spanning genomic nucleotides 511-6,944" (Edelmann 1023, col. 2).

2. Edelmann teaches that "[t]o determine the frequency of carriers for MLIV in the AJ population, we screened for both the major IVS3-2A→G and the minor 511del6434 mutations in genomic DNAs" (Edelmann 1024, col. 1).

3. Edelmann teaches that a "multiplex PCR amplification was performed . . . The primer sequences [were] designed to detect the major mutation MLIV-1UPS . . . and the primer sequences designed to detect the minor mutation were MLIV-3UPS" (Edelmann 1024, col. 1).

4. The Examiner finds that Edelmann teaches that the MLIV-3UPS primer is complementary to the "20 nucleotides from position 241 to position 260, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene" (Ans. 4).

5 The Examiner finds that Edelmann teaches that the MLIV-4UPS primer "is complementary to the 20 nucleotides from position 7017 to 7036, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene" (*id.*).

6. The Examiner finds that "Edelmann et al teaches the detection of the mutant sequence using a probe . . . complementary to nucleotides from positions 503-510 and positions 6944-6954, thus satisfying the limitations of the claim because the probe is complementary to a sequence

that is amplified from a template DNA that possesses the 511del6434" (Ans. 4).

7. Edelmann teaches that the "primers were designed from the genomic sequence of the *MCOLN1* gene (Sun et al. 2000; GenBank accession number AF287270)" (Edelmann 1024, col. 1).

8. Edelmann teaches that "[a]liquots (4 µl) of the PCR products were blotted . . . Hybridization was performed with the following allele-specific oligonucleotides (ASOs): for the IVS3-2A→G mutation . . . . and for the 511del6434 mutation" (Edelman 1024, col. 2).

9. Doll teaches a "rapid genotyping method to distinguish among the frequent and/or functional nucleotide polymorphisms in *NAT1*" (Doll 330, col. 1).

10. Doll teaches that "[n]ucleotide-specific polymerase chain reaction (PCR) primers and fluorogenic probes were designed using Primer Express (Version 1.5, Applied Biosystems, Foster City, CA)" (Doll 330, col. 1).

11. Doll teaches that "[m]ajor advantages of this genotyping method are that it does not require post-PCR processing or the use of radioactivity. . . . Since the new method does not require post-PCR processing, it is much faster and suitable for automated, high-through-put applications" (Doll 331, col. 1-2).

12. The Examiner finds that "[o]ne would have been motivated to do so based on the assertion by Doll et al that the real time PCR based method is a rapid method for the analysis of nucleic acid sequences that is

reliable, does not require radioactivity, and is suitable for automated applications" (Ans. 6).

13. The Examiner finds that "[o]ne would have had a reasonable expectation of success because Doll et al teaches the successful analysis of multiple nucleic acid mutations within a given nucleic acid sample . . . similar to the analysis of the multiple mutations of the MCOLN1 gene (Fig.2 of Edelmann et al)" (Ans. 6).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

"[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," *KSR* directs that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

Analysis

Claim 19

Edelmann teaches a PCR based method to detect the presence of a Mucolipidosis IV deletion mutation (FF 1-2) using primers and a probe which satisfy the requirements of step a) of claim 19 (FF 3-8). Doll teaches multiplex genotyping with Real-Time PCR (FF 9-10), specifically teaching that "[m]ajor advantages of this genotyping method are that it does not require post-PCR processing or the use of radioactivity. . . . Since the new method does not require post-PCR processing, it is much faster and suitable for automated, high-through-put applications" (Doll 331, col. 1-2; FF 11).

Applying the *KSR* standard of obviousness to the findings of fact, we agree with the Examiner that it would have been obvious to substitute the Real-Time PCR method of Doll for the standard PCR method of Edelmann since Doll teaches specific advantages of Real-Time PCR over the standard PCR method (FF 9-10). Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

We are not persuaded by Appellants' argument that "[n]either Edelmann et al. nor Doll et al. teach or suggest a method for the real-time detection of a deletion mutation in the MCOLN1 gene as required by claim 19" (App. Br. 8). Edelmann expressly teaches detection of the same deletion mutation which is detected in claim 19, the 511del6434 mutation, noting that "we screened for both the major IVS3-2A→G and the minor 511del6434 mutations in genomic DNAs" (Edelmann 1024, col. 1; FF 2). With this teaching by Edelmann of the specific mutation and the teaching by Doll that

Real-Time PCR is superior to standard PCR (FF 9-10), the prior art clearly suggests replacing standard PCR assays with Real-Time PCR (FF 9-10). As noted by the Court in *KSR*, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." 550 U.S. at 421.

We also are not persuaded by Appellants' argument that "[t]he Examiner fails to demonstrate that the prior art provides a motivation to combine the methods of Edelmann et al. and Doll et al. in an attempt to derive the method of claim 19." (App. Br. 8.) In *KSR*, the Supreme Court rejected the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, stating that

> The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

Id. at 417. Additionally, the Examiner has addressed motivation and explained that "[o]ne would have been motivated to do so based on the assertion by Doll et al that the real time PCR based method is a rapid method for the analysis of nucleic acid sequences that is reliable, does not require radioactivity, and is suitable for automated applications" (Ans. 6; FF 12).

Claim 25

We also do not find persuasive Appellants' argument that "the combination Edelmann et al. and Doll et al. fails to teach, and provides no reasonable expectation that multiple types of mutations (i.e., point mutations

and deletion mutations) can be simultaneously detected on multiple amplicons in a real-time PCR-based assay as recited in claim 25" (App. Br. 10). We find that Doll teaches commercially available primer selection software for Real-Time PCR (FF 10), and Edelmann and Genbank provide the complete DNA sequence of both the MCOLN1 gene and of the specific mutations within that gene (FF 1-7). The Examiner concludes that "[o]ne would have had a reasonable expectation of success because Doll et al teaches the successful analysis of multiple nucleic acid mutations within a given nucleic acid sample . . . similar to the analysis of the multiple mutations of the MCOLN1 gene (Fig.2 of Edelmann et al)" (Ans. 6; FF 13).

Kubin commented that "[r]esponding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court [in *O'Farrell*] stated: '[o]bviousness does not require absolute predictability of success ... *all that is required is a reasonable expectation of success*.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). Given that both Real-Time PCR and standard PCR were known methods, that Doll shows functional multiplex Real-Time PCR (FF 1-11), the evidence of record supports the Examiner's finding of a reasonable expectation of success (FF 13). Appellants provide no evidence to show why there would not have been a reasonable expectation of success (*see* App. Br. 10-11).

Conclusion of Law

Appellants have not demonstrated that the Examiner erred in finding it obvious to utilize the real-time PCR assay of Doll to detect the deletion and point mutations in the MCOLN1 gene disclosed by Edelmann.

B. 35 U.S.C. § 103(a) over Edelmann, Genbank, Doll, and Buck

The Examiner finds that "Edelmann et al teaches methods for detecting mutations in the MCOLN1 gene using primers and probes that are functionally equivalent (i.e. primers that amplify the relevant mutation-containing portions of the MCOLN1 gene, and probes that detect the particular mutations within the MCOLN1 gene) to the primers and probes required by the claims" (Ans. 7).

Appellants argue that "with respect to claims 23 and 31 which relate to the use of the oligonucleotide probe of SEQ ID NO.: 7, Appellants point out that the Examiner has failed to provide any reasons why the use of this probe, which is not disclosed in the prior art, is obvious" (App. Br. 12). Appellants argue that "Dr. Sun concludes that there is no expectation that any set of PCR primers, combined with any oligonucleotide hybridization probe will be successful in a real-time amplification assay" (*id.*).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Have Appellants demonstrated that the Examiner erred in finding it obvious that the claimed primers represent functional equivalents selected from the MCOLN1 sequence taught by Genbank for use in the real-time PCR assay of Doll to detect the deletion and point mutations in the MCOLN1 gene disclosed by Edelmann?

Findings of Fact

14. The Examiner finds that "GenBank AF287270 teaches the complete nucleic acid sequence of the MCOLN1 gene from humans, which includes the positions of the MLIV-4UPS, MLIV- 3UPS, MLIV-1 UPS, and

MLIV-2UPS primers and the 51ldel6434 probe from Edelmann et al, as well as SEQ ID NOs 1, 2, 3, 4 (paragraphs [0035]-[0036]; Table 1) and SEQ ID NO: 7 (paragraph [0050]; Table 2) from the instant application" (Ans. 7).

15. Buck teaches that the "results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality. . . . This study confirms earlier observations that there is a broad tolerance in these and other characteristics of sequencing primers" (Buck 535, col. 2) (citation omitted).

16. The Examiner finds that "[w]hen Buck et al tested each of the primers selected by the methods of the different labs, Buck et al found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well" (Ans. 8).

17. The Specification teaches that the first primer comprises "a sequence complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene" (Spec. 4 ¶ 0014).

18. The Specification teaches that the second primer comprises "a sequence complementary to a 15-30 bp segment of DNA between positions 6956 and 7356 of the MCOLN1 gene" (Spec. 4 ¶ 0014).

19. The Specification teaches that the oligonucleotide probe comprises "a sequence complementary to a 13-30 bp segment of a fragment that is amplified using the first and second oligonucleotide primers" (Spec. 4 ¶ 0014).

20. The Specification teaches that "[e]xemplary primers for amplifying segments of the MCOLN1 gene are given in Table 1. Additional

IVS forward primers include those that hybridize within a 400 bp stretch of DNA from position[s] 5124 to 5524 (accession # AF287270). Additional IVS reverse primers include those that hybridize within a 400 bp stretch of DNA from position[s] 5141 to 5941 (accession # AF287270)" (Spec. 9 ¶ 0035).

21. The Specification teaches that the "probe for detecting the amplified fragment that results following deletion of 6.4 kb may hybridize anywhere within this amplified fragment" (Spec. 14 ¶ 0050).

Principles of Law

An "obviousness finding was appropriate where the prior art 'contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" *In re Kubin*, 561 F.3d at 1360 (citing *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988). The court commented that "[r]esponding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court [in *O'Farrell*] stated: '[o]bviousness does not require absolute predictability of success … *all that is required is a reasonable expectation of success*.'" *Kubin*, 561 F.3d at 1360 (citing *In re O'Farrell*, 853 F.2d at 903-904).

Analysis

As in *Kubin*, the issue is whether the claimed primer and probe sequences, as used in the Real-Time PCR method, are obvious in light of Edelmann, Doll, Genbank and Buck.

In the instant case, Appellants own Specification recognizes that the primers for the Real-Time PCR assay may be selected from any oligonucleotides of 15 to 50 nucleotides in length which hybridize to a 400 basepair regions at each side of the relevant deletion mutation (FF 17-21). The Specification clearly does not suggest any criticality to the particular primers exemplified, nor does the Specification provide any comparative data or other evidence to show any unexpected results or properties for these particular primers (FF 17-21).

Edelmann provides strong reasons "[t]o determine the frequency of carriers for MLIV in the AJ population, we screened for both the major IVS3-2A→G and the minor 511del6434 mutations in genomic DNAs" (Edelmann 1024, col. 1; FF 2). Doll provides reasons to use Real-Time PCR (FF 9-10). Both Buck and the instant Specification demonstrate that primer selection is a standard and known procedure in biotechnology and Buck exemplifies the expectation of success in primer selection (FF 16-21).

In comparing the obviousness of the instant primers to the obviousness issue in *Kubin*, we note that unlike in *Kubin* where the NAIL DNA sequence was unknown, the complete DNA sequence from which the instant primers were selected was disclosed in Genbank and referenced by Edelmann (FF 1-8). Additionally, Doll teaches that computer software to aid in selection of the primers for the specific Real-Time PCR assay was commercially available and was successfully used to select primers for a different genetic disease (FF 9-10).

Thus, if *Kubin* finds that cloning an unknown gene sequence had a "reasonable expectation of success," we conclude that it is more than

reasonable to find that selection of particular Real-Time primer sequences from a known sequence using commercially available software "would have had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art." *Kubin*, 561 F.3d at 1360. This is particularly the case when Appellants own Specification suggests that primers anywhere within the regions around the deletion and probes anywhere within the deletion may be used and would have been expected to function (FF 17-21).

We are not persuaded by Appellants' argument that "the Examiner has failed to provide any reasons why the use of this probe, which is not disclosed in the prior art, is obvious" (App. Br. 12). When Appellants argue that the probe is not disclosed by the prior art, they mean that while the probe sequence is found within the disclosed Genbank Sequence and while their own Specification teaches that a functional probe "may hybridize anywhere within this amplified fragment" (Spec. 14 ¶ 0050; FF 21), the Examiner has not specifically identified why the specific claimed sequence was selected out of the many equivalent possible probes, all of which would have been expected to function based upon the disclosure of both the prior art and Appellants own Specification (FF 17-21). We find that all of these equivalent probes are obvious, since all of the probes would have been expected to function in the detection of the Mucolipidosis deletion mutation. "[A]rtisans in this field, as found by the Board in its expertise, had every motivation to seek and every reasonable expectation of success in achieving the sequence of the claimed invention. In that sense, the claimed invention

was reasonably expected in light of the prior art and 'obvious to try.'" *Kubin*, 561 F.3d at 1361.

We have considered the Declaration by Dr. Sun. However, Dr. Sun argues that the specific primers of Edelmann might not work in Real-Time PCR (*see* Sun Dec.[1] ¶ 5), but does not recognize that the obviousness inquiry is whether the ordinary practitioner would have selected functional primers from the known Mucolipidosis gene sequence for use in Real-Time PCR, not whether the specific primers already disclosed would function in Real-Time PCR. Dr. Sun provides no evidence that the primers of Edelmann do not work in Real-Time PCR (*see* Sun Dec. ¶ 5-7), and we find no persuasive evidence or argument on this record to suggest that a person of ordinary skill in this art would not have known to select functional primers from the known Mucolipidosis gene sequence for use in the Real-Time PCR methodology taught by Doll.

Mechanistically, the Edelmann PCR primers, the Buck sequencing primers, and Doll Real-Time PCR primers and Appellants' claimed primers, all operate using the same principles. The methods require that the single stranded oligonucleotide primers hybridize to their single stranded complement in a target DNA, where a thermostable DNA polymerase then binds the primer/target DNA complex and extends the primer along the target to form a double-stranded DNA with fully complementary sequence (*see*, e.g., Spec. 9 ¶ 0034). Supporting a finding of a reasonable expectation of success, Buck provides evidence that virtually all primers selected from a

[1] Declaration of Weiman Sun, Ph.D., dated August 9, 2006.

target sequence are capable of undergoing hybridization and extension by a polymerase (FF 16).

In the same context, Doll teaches that commercial software is available which assists in the specific selection of primers for Real-Time PCR (FF 10), which would reasonably provide a significant expectation of success in the assay. In fact, Doll utilized this software and successfully selected primers which functioned in a Real-Time PCR assay to detect a set of mutations in a multiplex format (FF 9). Consequently, this is a situation where the prior art "provides a 'reasonable expectation of success' for obtaining a polynucleotide within the scope of [the] claim . . . which, '[f]or obviousness under § 103 [is] all that is required.' *O'Farrell*, 853 F.2d at 903." *Kubin*, 561 F.3d at 1361.

Finally, Appellants have not proffered any evidence of a secondary consideration which would address or overcome the Examiner's prima facie case of obviousness.

Conclusion of Law

Appellants have not demonstrated that the Examiner erred in finding it obvious that the claimed primers represent functional equivalents selected from the MCOLN1 sequence taught by Genbank for use in the real-time PCR assay of Doll to detect the deletion and point mutations in the MCOLN1 gene disclosed by Edelmann.

SUMMARY

In summary, we affirm the rejection of claims 19 and 25 under 35 U.S.C. § 103(a) over Edelmann, Doll, and Genbank. Pursuant to 37 C.F.R.

§ 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 23, 24, 28, and 32-34 as these claims were not argued separately.

We affirm the rejection of claim 20 under 35 U.S.C. § 103(a) over Edelmann, Doll, Genbank, and Buck. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 21, 22, 26, 27, and 29-31 as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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